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Remarks:
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(54) Use of glutathione esters for the treatment of pulmonary diseases

(57) Glutathione esters are used in the manufacture of a composition for administration to a patient for the treatment of pulmonary disease, such as sepsis syndrome and adult, or infant respiratory distress syndrome.

EP 0 715 853 A1

Description

BACKGROUND OF THE INVENTION

The present invention relates generally to the treatment of pulmonary disease. More specifically, the present invention relates to the preparation of compositions that can be used for the treatment of diseases that result in acute and/or chronic respiratory distress.

There are a number of pulmonary or respiratory disease states that can cause acute or chronic respiratory distress and result in damage to the lungs of the patient. Resulting damage can be debilitating to the patient and on occasion result in death.

Adult respiratory distress syndrome (ARDS) is a common medical emergency that is precipitated by a variety of acute processes that directly or indirectly injure the lungs. For example, ARDS can be precipitated by primary bacterial or viral pneumonias, aspiration of gastric contents, direct chest trauma, prolonged or profound shock, burns, near drowning, fat embolism, blood transfusions, cardio-pulmonary bypass, O_2 toxicity, or acute hemorrhagic pancreatitis. ARDS usually develops within twenty-four to forty-eight hours after initial injury or illness. It is believed that activated leukocytes and platelets accumulate in the capillaries, interstitium, and airspaces. They may release products including prostaglandins, toxic O_2 radicals, proteolytic enzymes, and other mediators that injure cells, promote fibrosis, and alter bronchomotor tone and vasoreactivity. See, The Merck Manual, Fifteenth Edition.

Injury to the pulmonary capillary endothelium and alveolar epithelium causes plasma and blood to leak into the interstitial and intra-alveolar spaces. Flooding of the alveolae and atelectasis results. Typically, within two or three days, a second phase of lung injury is characterized by bronchoalveolar inflation. Additionally, there is proliferation of epithelial and interstitial cells. Typically, in a third phase collagen accumulation may progress rapidly. This can result in severe interstitial fibrosis within two to three weeks. This pathological change, can lead to low lung compliance, pulmonary hypertension, decreased functional residual capacity, ventilation/perfusion maldistribution, and hypoxemia.

Unfortunately, the survival rate for severe ARDS is less than 50% with appropriate treatment. Although the mechanism of lung injury in adult respiratory distress syndrome is not certain, data from animal models and indirect evidence from studies in human beings has suggested that toxic oxygen metabolites produced by stimulated neutrophils are a possible agent of the alveolar injury. Baldwin, et al, Oxidant Activity In Expired Breath of Patients With Adult Respiratory Distress Syndrome, The Lancet, January 4, 1986, pages 11-13.

Because it has been hypothesized that oxygen free radicals released during endotoxemia may contribute to the lung injury of ARDS, the effect of intravenous n-acetylcysteine, a free radical scavenger, on the endotoxin induced model of ARDS in awake sheep has been investigated. Bernard, et al., Effect of N-acetylcysteine on the Pulmonary Response to Endotoxin in the Awake Sheep and Upon In Vitro Granulocyte Function, J. Clin. Invest., Vol. 73, pp 1772-84 (1984). The paper states that n-acetylcysteine inhibits granulocyte aggregation and scavenges free radicals in vitro. The paper postulates, therefore, that the beneficial effect of n-acetylcysteine in attenuating the pathophysiologic processes seen in the sheep model of the adult respiratory syndrome is due to its ability to scavenge oxygen free radicals in vivo.

Lucht, et al., Prevention of Release of Granulocyte Aggregants Into Sheep Lung Lymph Following Endotoxemia By Acetylcysteine, The American Journal of the Medical Sciences, Vol. 294 No. 3 (September 1987), discusses experiments wherein n-acetylcysteine was administered to sheep before endotoxin infusion. The paper concludes that endotoxemia causes the release from the lungs of substance(s) that activate granulocytes, and that this response is prevented by n-acetylcysteine, possibly as a result of the antioxidant properties of the drug.

Although, attention has focused on treating and/or curing ARDS, an effective treatment is still not available.

Infant respiratory distress syndrome, or IRDS, is a disorder primarily of prematurity, manifested clinically by respiratory distress and pathologically by pulmonary hyaline membrane disease and atelectasis. See Merck Manual, Fifteenth Edition. IRDS results from diffuse lung atelectasis due to a deficiency of pulmonary surfactants at birth. Due to pulmonary insufficiency, these neonates are placed in hyperoxic (95% O_2) environments. The inability to produce adequate amounts of glutathione exacerbates the oxidative stress and damage to the lungs. If untreated, IRDS can result in bronchopulmonary displasia, blindness, brain damage, multiple organ failure and death.

Other disease states, such as cystic fibrosis, idiopathic pulmonary fibrosis, and emphysema, also can result in lung damage due to cell damage from oxidation. The lungs are exposed to oxidative stress due to airborne oxidants and to hyperoxygen stress when respiratory treatment includes elevated oxygen (e.g., 95% O_2) treatment. Additionally, inflammatory cells, macrophages, neutrophils, and the like, secrete active oxygen species in the lungs.

SUMMARY OF THE INVENTION

The present invention relates to use of a glutathione ester in the manufacture of a composition for treating pulmonary disease in a patient suffering from same.

It has been found, that by increasing glutathione levels within a cell, the pulmonary cells will experience reduced damage when exposed to oxidative stress. Cells having depressed glutathione levels are susceptible to membrane lipid

peroxidation, mitrochandrial damage, and progressive fibrosis of lung tissue. However, turnover of glutathione and of endogenous antioxidants in pulmonary endothelium is very rapid.

Glutathione esters are utilized according to the invention to elevate tissue glutathione levels within the cells.

The present invention provides for the use of the composition to treat adult respiratory distress syndrome or infant respiratory distress syndrome which result in oxidative stress that can damage the cells of the lung.

The composition may be administered parenterally, or enterally.

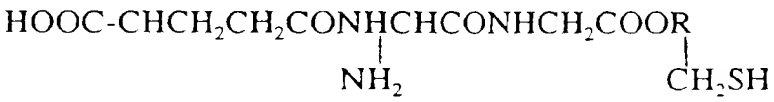
Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments.

DETAILS DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

Glutathione esters are non-cysteine compositions and are distributed effectively in tissues of the patent. It is believed that the enzymes necessary for deacetylization of an acetylated compound such as n-acetylcysteine exist only in the Kidney. Accordingly, a compound such as n-acetylcysteine must be metabolized to cysteine in the kidney then transported to the liver or peripheral cells. Therefore, such compounds may not be sufficiently distributed to the requisite tissues of the patient, i.e. the tissue of the lungs.

Furthermore, the composition is not itself an anti-oxidant. Although it may be desirable to introduce an anti-oxidant into a patient having adult respiratory distress syndrome to prevent damage from the oxygen radicals, anti-oxidants are not stable.

The glutathione ester may have the structure:-



wherein R is an alkyl group containing 1 to 10 carbon atoms. Preferably, the methyl and ethyl glutathione esters are used. It is also preferred to use glutathione isopropyl ester. Glutathione esters are disclosed in US Patent No 4,784,685, the disclosure of which is incorporated herein by reference.

Embodiments of the invention include:-

a) A buffered (pH 6.5 - 6.8) 3% or 6% glutathione ester aqueous solution.

b) A buffered 3% or 6% glutathione ester aqueous solution containing any of the following alone or in appropriate combinations: amino acids, dextrose or other carbohydrate sources, and lipid emulsions.

c) A vial containing a crystalline or lyophilized glutathione ester to which appropriate aqueous solutions are added at time of use.

d) A gelatin capsule containing a crystalline or lyophilized glutathione ester.

e) A pill containing a crystalline or lyophilized non-cysteine glutathione precursor.

f) A liquid elemental, protein hydrolysate, carbohydrate and/or lipid emulsion containing enteral dietary supplement containing glutathione ester.

The composition can be administered as an adjunct therapy with other typical therapies. For example, steroids, non-steroid anti-inflammatories, prostaglandin synthesis inhibitors (ibuprofen), mucolytics, tumor necrosis factor antibodies, artificial surfactants (Exosurf, Survanta), hyperoxic and ventilation therapies, and antibiotics can be administered with the glutathione ester.

By way of example, but not limitation, contemplated examples of the use of glutathione precursors will now be given.

EXAMPLE 1

A 55-year-old patient with sepsis syndrome that progressed into ARDS was given an intravenous administration of a neutral (pH 6.5 - 6.8) 6% solution of L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d. for 10 days. It should be noted that a continuous infusion of a 6% solution equivalent to 45 mg/kg/day could have been used as an alternative dosing regimen. The infusion although by independent intravenous administration, could have been through an indwelling intravenous catheter.

The patient demonstrated the following physiological characteristics at the start and end of treatment:

Physiology	Start	End
PaO_2/PAO_2	0.24	0.38
Cardiac Output (liters/min)	5.65	7.93
Thoracic Static Compliance (ml/cm H_2O)	34.4	42.3
Chest Radiograph of Pulmonary Edema (0 = normal, 3 = severe)	2.5	1.1
Plasma Glutathione (nmoles/ml)	2.47	7.96
Red Cell Glutathione (nmoles/ml)	2,753	5,825
Lung Glutathione (nmoles/ml by Bronchoalveolar lavage)	84	398

EXAMPLE 2

A neonate born at 27 weeks gestational age, weighing 984 grams, and suffering from Hyaline membrane disease was placed in a ventilator and given Exosurf (95cc/kg) at 18 and 30 hrs of age. The patient received an intravenous administration of a neutral (Ph 6.5 - 6.8) 3% L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d., as a continuous infusion. A 6% solution equivalent to 45 mg/kg could have also been administered. The administration was continued until the infant has sufficiently developed to demonstrate adequate blood oxygenation in a normoxic environment, without mechanical or artificial ventilatory support.

The neonate displayed the following ventilatory requirements at entry and at 28 days:

	Entry	Day 28
Oxygenation index	1.48	0.62
Ventilation rate	920/24hr	223
FiO_2	1184/24hr	774
Positive end-expiratory pressure	104/24hr	31
Mean airway pressure	208/24hr	56
(Values are summation of area under curve for 24 hour measurements).		

At 28 days the patient was scored 1.5 for bronchopulmonary displasia, 1.0 for retrolental fibroplasia and 0.5 for intraventricular hemorrhage on a 0 to 5 scale (0 being normal, 5 being severe).

EXAMPLE 3

An 18-year-old hospitalized cystic fibrosis patient received intravenous tobramycin and ceftazidine every eight hours for 6 days. The patient received an intravenous administration of a neutral (pH 6.5 - 6.8) 3% L-2-oxothiazolidine-4-carboxylate equivalent to 15 mg/kg, t.i.d. during continuous infusion. Alternatively, a 6% solution equivalent could have been administered. Although administration occurred during in-patient treatment it could have occurred using home intravenous drug therapy. Administration of the non-cysteine glutathione precursor occured by independent injection at infusion, but could have taken place by infusion through an indwelling intravenous catheter.

The following changes in physiological characteristics were recorded at termination of treatment;

SaO_2	+3.6%
Weight (% increase)	+4.5%
FVC (%predicted)	+15.9%
FEV1 (% predicted)	+14.3%
Bronchoalveolar lavage glutathione	+322%

The patient with cystic fibrosis also receive an enteral dose of the non-cysteine glutathione precursor equivalent to 15 mg/kg, t.i.d., as a prophylactic treatment during periods free of acute respiratory infection. The enteral dose was given as a capsule, but could have been given as a pill, liquid, or as part of a nutrient containing liquid enteral diet, or as a combination of these delivery methods.

EXAMPLE 4

A 68-year-old malnourished patient with an acute exacerbation of emphysema is admitted to the respiratory ICU. The patient requires mechanical ventilation and nutritional support. An enteral diet containing 18% protein, 27% CHO, 55 fat is provided at 1.3 times the resting energy expenditure. The diet was supplemented with 15 mg/kg of a non-cysteine glutathione precursor in 250 ml of diet. The patient was successfully weaned from the ventilator and diet on day 8. Lung lavage glutathione levels were taken at admission and on day 7:

	Admission	Day 7
$PaCO_2$	6.09	5.15
$PaCO_2/PAO_2$	31.5	38.4
Ventilation rate (b/m)	31	24
Minute volume (l/m)	16.5	14.2
Glutathione (umol/ml)	95	402

It is anticipated that a patient with emphysema would receive an enteral dose of a non-cysteine glutathione precursor equivalent to 15 mg/kg, t.i.d., during periods of acute exacerbations, and as a prophylactic treatment during quiescent periods. The enteral dose could be given as a capsule, pill, liquid, or as part of a nutrient containg liquid enteral diet, or as a combination of these delivery methods.

Claims

1. Use of a glutathione ester for the preparation of a composition for treating pulmonary disease in a patient suffering from same.

2. Use of a glutathione ester for creating a composition for treating a respiratory distress syndrome in a patient suffering from same.

3. The use according to Claim 2 for treating a patient with sepsis syndrome.

4. The use according to Claims 1 or 2, for treating a patient with adult respiratory distress syndrome.

5. The use according to Claim 1 or 2, for treating a patient with infant respiratory distress syndrome.

6. The use according to Claim 1 for treating a patient with cystic fibrosis.

7. The use according to Claim 1 for treating a patient with emphysema.

8. The use according to Claim 1 for treating a patient with idiopathic pulmonary fibrosis.

9. The use according to Claim 1 or 2, for treating Hyaline membrane disease.

10. The use according to Claim 4 for treating a patient with adult respiratory distress syndrome precipitated by primary bacterial or viral pneumonia, aspiration of gastric contents, direct chest trauma, prolonged or profound shock, burns, near drowning, fat embolism, blood transfusion, cardiopulmonary bypass, oxygen toxicity or acute haemorrhagic pancreatitis.

11. The use according to Claim 1 or 2, wherein the composition is administrable parenterally.

12. The use according to Claims 1 or 2, wherein the composition is administrable enterally.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 20 0042

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
A	PROC. NATL. ACAD. SCI. USA, vol. 86, no. 14, 1989 pages 5296-5300, XP 000566919 J. MARTENSSON ET AL. 'Glutathione metabolism in the lung: in hibition of its synthesis leads to lamellar body and mitochondrial defects.' ---		A61K38/06
A	ARCH. BIOCHEM. BIOPHYS., vol. 239, no. 2, 1985 pages 538-548, XP 000567250 M.E. ANDERSON ET AL. 'Glutathione monoethyl ester: preparation, uptake by tissues and conversion to glutathione.' ---		
A	HEPATOLOGY, vol. 4, no. 4, 1984 pages 739-742, XP 000567259 A. MEISTER 'New developments in glutathione metabolism and their potential application in therapy.' ---		TECHNICAL FIELDS SEARCHED (Int.Cl.5)
A	BIOCHEM. INT., vol. 18, no. 2, 1989 pages 439-446, XP 000567272 S. HONDA ET AL. 'Protective effect of glutathione against oxygen-induced growth inhibition of human diploid fibroblasts.' ---		A61K
A	US-A-4 784 685 (MEISTER) 15 November 1988 -----		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 March 1996	Klaver, T

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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E : earlier patent document, but published on, or after the filing date
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